Introduction

Antimicrobial drugs are used in food-producing animals to treat, prevent and control disease and to improve growth and feed efficiency. In the United States, these products are considered new animal drugs. Before any new animal drug can be approved in the United States, the drug's sponsor must demonstrate that the product is safe and effective for its intended use. If the antimicrobial is intended for use in food producing animals, the drug sponsor must demonstrate safety for consumers of edible animal products, as well as safety for use in the animal.

Animals may be reservoirs of bacteria that can cause disease in humans. Many such zoonotic pathogens may be present in food, including *Salmonella* and *Campylobacter*, and are naturally present in the gastrointestinal tract of food-producing animals. When an animal is treated with an antimicrobial drug, a selective pressure is applied to all bacteria associated with that animal. Bacteria that are sensitive to the antimicrobial are killed, while bacteria that have the ability to resist the antimicrobial can persist and replace the sensitive bacteria. In addition, bacteria can become resistant when resistance genes are passed from a resistant bacterium to a sensitive one. Thus, antimicrobial agents may increase the prevalence of resistant bacteria among both target pathogens and normal bacterial flora.

The magnitude of the public health risk associated with antimicrobial use in animals has been debated for over thirty years. In the early 1990's, several scientists expressed concern that the approval of fluoroquinolones for use in food producing animals in the United States would result in fluoroquinolone resistant food borne disease in humans. Since the approval of fluoroquinolones for food producing animals, reports have identified a relationship between the approval of fluoroquinolones for therapeutic use in food producing animals and the development of fluoroquinolone resistance in *Campylobacter* in animals and humans. The approval of these drugs in food-producing animals in the Netherlands, (24, 41, 61) and Spain (60, 90) temporally preceded increases in resistance in *Campylobacter* isolates from treated animals and ill humans. Despite several restrictions placed on the use of the two approved poultry fluoroquinolone products in the United States, fluoroquinolone-resistant *Campylobacter* were recently isolated from 20 percent of domestic retail chicken products that were sampled. Molecular subtyping revealed an association between resistant *C. jejuni* strains from chicken products and *C. jejuni* strains from domestically acquired human cases of campylobacteriosis (71). To date, fluoroquinolone resistance has not been observed in *Salmonella* species associated with poultry although a slight loss in susceptibility has been noted (19).

Based upon emerging scientific evidence that therapeutic uses of antimicrobials in food-producing animals, in addition to subtherapeutic feed uses, may select for resistant bacteria of human health concern, the FDA announced in November 1998 draft regulatory guidance in this area (available at http://www.fda.gov/cvm/). This guidance states that FDA believes it is necessary to consider the potential human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals when approving such drugs. In December 1998, CVM issued a discussion document entitled "A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals." This document stated FDA's position that the regulatory system for antimicrobials for use in food producing animals should be modified to address microbial safety concerns. To assess microbial safety, the document discussed the need to consider both the importance of the drug to human medicine and the potential human exposure to resistant bacteria acquired from food producing animals that are human pathogens or that can transfer their resistance to human pathogens. The document went on to articulate the need to determine acceptable levels of resistant bacteria in animal products (thresholds) to ensure that the effectiveness of human antimicrobials would not be compromised.

To assist in evaluating the human health impact of antimicrobial use in animals, the Center contracted with a risk assessment expert to develop a risk assessment model. The risk assessment was intended to determine the feasibility of estimating risk to human health from resistant food borne pathogens associated

with the use of antimicrobials in food producing animals. Specifically, a mathematical model was derived to relate the prevalence of fluoroquinolone resistant *Campylobacter* infections in humans associated with the consumption of chicken to the prevalence of fluoroquinolone resistant *Campylobacter* in chickens. The model could become a regulatory tool for assessing such risks in the future.

The use of fluoroquinolones in chickens and the development of resistant *Campylobacter* in chickens were of concern for several reasons. First, chickens are reservoirs for many food borne pathogens including *Campylobacter* and *Salmonella*. For example, broiler carcass contamination measured in the processing plant estimates that 20% of broiler chickens in the United States are contaminated with *Salmonella* and over 80% are contaminated with *Campylobacter*. Consumption of food contaminated with these bacteria can lead to illness in susceptible individuals. Second, *Campylobacter* is the most common known cause of bacterial food borne illness in the United States. (74) Sporadic cases of *Campylobacter* account for approximately 99% of all *Campylobacter* cases. Epidemiological investigations of sporadic infections have indicated that chicken is the most common source of human infection (2, 71, 74) Also, slaughter and processing of chickens may result in bacterial contamination on the carcass that can survive on retail product and result in human exposure during food preparation and consumption. Third, *Campylobacter* has been reported to develop resistance quickly when fluoroquinolones are used in both human and veterinary medicine. Finally, fluoroquinolones are used in human medicine empirically to treat gastrointestinal infections, such as campylobacteriosis and are important for use in many other therapeutic indications in human medicine.

Food Borne Disease and Microbial Risk Assessments

Food borne diseases caused by bacteria have a major public health impact in the United States. Recent estimates describe 5,000 deaths and 76 million cases of food borne illness annually (51). A 1994 report estimated an annual economic burden due to food borne illness at 22 billion dollars (21).

Campylobacter is the most common known cause of bacterial food borne illness in the United States. (74) The incubation period for campylobacteriosis is 1 day to 1 week and infections usually result in mild to moderate symptoms including diarrhea, abdominal pain and fever. Symptoms may last 1 day to 1 week or more, and in up to 20 percent of cases, illness lasts for more than a week. Although most cases of campylobacteriosis are self-limiting, some patients experience symptoms sufficiently severe to seek care and take antibiotics for their illness. Relapses occur in approximately 5 to 10% of untreated patients. More invasive disease such as blood infections occur in less than 1% of patients with *C. jejuni* infections and are more common in the elderly or very young individuals. Rare manifestations of *C. jejuni* can include meningitis, endocarditis and septic abortion. Persons with immunoglobulin deficiencies may manifest prolonged, severe and recurrent infections (9). Campylobacteriosis has been associated with chronic sequelae that include reactive arthritis, inflammation of the liver and kidney and Guillain-Barré syndrome, a demyelinating disease that may result in a reversible paralysis (9).

While the safety assessments for food additives, veterinary drugs and pesticides are very standardized and accepted internationally, microbial risk assessments are relatively new, with no formal procedures. Microbial food safety problems are generally extremely complicated and assessment requires a great deal of data. To date, about a half-dozen microbial risk assessment models have been published that attempt a full quantitative assessment of the public health risks of microbial contamination. These models use only very specific products and very limiting assumptions and have not been used by regulatory agencies to set limits on the amount of bacterial contamination permitted in food. Under the President's Food Safety Initiative, the charge to government agencies with respect to risk assessment was to develop better data and modeling techniques to help characterize the nature and size of risks to human health associated with foodborne hazards (4).

Antimicrobial Resistance in Food Borne Disease

Emergence of antimicrobial resistant and multi-drug resistant bacteria are evident in both human and veterinary medicine. Bacterial food borne disease is a growing problem worldwide and has been addressed in many reviews and reports on the topic. Resistant food borne pathogens may be present in or on animals

as a result of drug use in animals. When these resistant food borne pathogens contaminate a carcass at slaughter, resistant bacteria can be transmitted to humans through consumption and handling of contaminated food. When these resistant bacteria cause illness in a consumer who needs treatment, medical therapy may be compromised if the pathogenic bacteria are resistant to the drug used for treatment. In industrialized countries, the food borne pathogens, *Salmonella* and *Campylobacter* are infrequently transferred from person to person. In these countries, epidemiological data has demonstrated that a significant source of antibiotic resistant food borne infections in humans is the acquisition of resistant bacteria from animals via food (24).

Although *Campylobacter* infections are usually self-limiting, antibiotic therapy is used for patients: 1) who demonstrate symptoms of high fever, bloody diarrhea, or more than eight stools in 24 hours; 2) who are immunosuppressed; 3) who have bloodstream infections; or 4) whose symptoms worsen or persist for more than 1 week. Antimicrobial therapy can reduce the median duration of illness (5, 20). Fluoroquinolones are frequently used empirically to treat *Campylobacter* illness. Empiric treatment of patients with enteric disease seeking treatment is the norm because when treatment is delayed (e.g., until *C. jejuni* infection is confirmed by a medical laboratory), therapy may not be effective. Fluoroquinolone drugs are frequently used in the empiric treatment of patients presenting to a physician with gastrointestinal symptoms because they exhibit good activity against most enteric pathogens. (9, 65)

Assessing the Public Health Impact of Antimicrobial Drug Use in Animals

The risk assessment model developed assumes that resistance in food animals is attributable to drug use, and that resistant bacteria pass through the food supply, infect humans and are treated in the same manner as susceptible bacteria. The health risk associated with antimicrobial resistant bacteria represents an incremental increase in risk to consumers because resistance to an antimicrobial used in human medicine can compromise the effectiveness of therapy. Using this approach, the incremental human health impact of resistant food borne disease can be determined without assessing all the factors influencing the cause of the food borne disease itself.

To limit the complexity of the assessment, only the public health risk associated with the use of fluoroquinolones in chickens was assessed. Fluoroquinolones were chosen because of their importance in treating enteric infections in humans. Information from USDA and CDC on sources of food borne disease indicated that chicken carcasses carry a relatively high level of *Campylobacter* and cause a large number of cases of food borne illness.

The model consists of five sections. Section 1 estimates the number of *Campylobacter* culture confirmed cases that would have been observed by US healthcare providers using FoodNet data extrapolated out to the entire US population.

Section 2 explains the extrapolation from the number of culture confirmed cases in the United States to the total number of campylobacteriosis cases in the US in a specified year including uncertainty in these estimates. The model gives a mean estimate number of 2.48 million cases of campylobacteriosis and a 90% confidence interval of 1.3 to 4.3 million cases. The large degree of uncertainty in the estimates reflects the compounding uncertainty from each parameter of the model.

Section 3 estimates the number of individuals that acquire fluoroquinolone-resistant infections associated with consuming chicken and subsequently receive fluoroquinolone treatment. The results of this section showed that in 1998 about 5000 people were infected with fluoroquinolone resistant Campylobacter from consuming chicken and received fluoroquinolones as therapy. The model gives a 90% confidence interval of 2585 to 8595 culture confirmed cases. It was assumed that all individuals with a fluoroquinolone resistant infection would experience a longer illness when treated with a fluoroquinolone due to a decrease in effectiveness of the drug. The fairly long length of the confidence interval is reflective of the lack of certainty in the various parameters used in the model in this section.

Section 4 estimates the pounds of boneless product carrying fluoroquinolone resistant *Campylobacter* consumed in a year. The mean value for this estimate is 1,450,000,000 with a 90% confidence limit of 967,000,000 and 1,990,000,000.

Section 5 discusses how the model can be used to manage the risk, proposes options for measuring the risk and strategies for controlling the risk.

Although the predominant interest to readers of this risk assessment may be to quantify the risk, it is important that the level of risk be viewed in context of the data used. This risk assessment has provided insight into the strengths and limitations of the data available to assess the impact of fluoroquinolone resistant *Camplyobacter* associated with consumption of chicken on human health. While assembling the data to be used in the risk assessment, numerous scientific limitations were raised and were addressed as data gaps where issues were considered relevant. Some issues were considered less relevant to determining the measurable impact of risk because methods have not yet been developed or are not practical due to cost or time considerations. One of the benefits of this assessment is that it has resulted in a review of how surveillance data is collected and identified what measurements are most relevant for linking the impact of resistant foodborne pathogens to human health.

The strengths of this model include the fact that it is mathematically simple and can be updated, as new data become available. The model can be readily adapted into a regulatory system for protecting the public health. The model does have limitations. It cannot directly prove a link between the level of resistance in bacteria from food producing animals and drug use in animals. However, it was considered to be justifiable to assume that the presence of resistant C*ampylobacter* on the animal carcass was due to antimicrobial drug use in the animals. Another limitation in the model is that prediction of the human health impact of changes in the level of carriage of resistant *Campylobacter* must be inferred, because one can not wait until sufficient bacteria are resistant to more accurately assess the human health impact of changes in the level of resistance. Finally, use of the model as a regulatory tool may be limited as the results contain significant levels of uncertainty. Some scientists have questioned the utility of using risk assessments with a lot of uncertainty to set public health standards because of the difficulty in evaluating the effectiveness of measures established to protect public health. However, by using this mathematically simple model, regulating on a sensitive endpoint and recalculating the model as new information becomes available, this model can serve as a tool to help the agency protect the public health.

Risk and strategies for controlling the risk

To ensure that this model can be used effectively to protect the public health, risk managers must determine the level of risk that expresses a quantitative definition of acceptable risk. In the past, these types of definitions have been established through public notice and comment rule making.

Once a quantitative definition of acceptable risk is established, the next step is to determine the harm or human health impact. In the Framework document, the agency defined the potential human health impact associated with the use of an antimicrobial drug in food producing animals as the loss of effective drugs to treat human disease. The agency considered that evaluation would be made of the availability of effective alternative therapies to treat a particular disease. This risk assessment model looks at the use of an empiric therapy, fluoroquinolones to treat a food borne disease, and does not explicitly consider the issue of effective alternative therapies. However, as a regulatory tool, we can use the risk assessment approach to consider harm several different ways. The risk assessment can define the harm associated with acquiring a resistant food borne as: 1) having a resistant infection; 2) having a resistant infection and receiving the antibiotic; 3) having the resistant infection, receiving the antibiotic and experiencing an adverse effect, such as a change in duration of illness; or 4) having the resistant infection, receiving the antibiotic and having no alternative drug to treat the infection. The last approach is most consistent with the definition articulated in the Framework document.

The final risk management decision is to define the target population(s) that need protection. The level of risk changes from 1 in 61,093 to 1 in 32 depending on whether the denominator is the total US population or persons with campylobacteriosis seeking care and prescribed an antibiotic (Table I.1).

People will perceive the size of the risk differently in different circumstances. For the average US citizen, the risk may well be perceived presently as being very small: we have estimated that 1 in 61,093 people were affected in 1998, for example. On the other extreme, people with reduced immunity who may be more likely to seek medical help, may perceive the risk as quite significant. The appropriate measure of this risk is vital to determine the appropriate resistance threshold. Four possible denominators are offered for discussion.

Table I.1 Level of Risk Determined for Various Denominators

Denominators	**Probability**	**Equated to 1 in:**
US citizen ($=n_{us}$)	0.0019%	61,093
Person with campylobacteriosis ($=N2_T$)	0.2265%	521
Person with campylobacteriosis seeking care ($=N2_{en}*p_{nm}+N2_{eb}*p_{bm}+N2_i$)	1.739%	63
Person with campylobacteriosis seeking care and prescribed antibiotic ($=(N2_{en}*p_{nm}*p_{an}+N2_{eb}*p_{bm}*p_{ab}+N2_i$)	3.384%	32

The probability column of Table I.1 gives an estimate of the probability that an individual will experience an effect associated with resistant campylobacteriosis. The first denominator distributes the risk among the entire US population. The second denominator distributes the risk among people who contract campylobacteriosis from any source. The third denominator distributes the risk among those people who contract campylobacteriosis from any source and then seek some medical care. The fourth denominator distributes the risk among those people who contract campylobacteriosis from any source, seek some medical care and are prescribed an antibiotic.

The current standard used by the FDA for food additives, including new animal drug residues, focuses on protecting the 90th percentile consumer. Recently, however, there has been increased interest and Congressional mandates to protect subpopulations such as children.

Using the model to manage the human health impact

This risk assessment estimates the human health impact arising from the observed fluoroquinolone-resistant *Campylobacter* prevalence in broiler carcasses. It effectively derives a ratio (given the label k and described in detail in Section 5) between the number of affected people ($N3_T$ in the model) and the volume of contaminated meat (V_i in the model). The model as it stands provides a quickly and continuously updateable method of estimating the current human health impact. There is considerable uncertainty in estimating the ratio k because of imperfect data, but further data and more years of monitoring would improve this estimate.

In use as a regulatory tool, it is necessary to be able to estimate the *future* human health impact, particularly if a rapid rise in resistance is observed or expected in poultry. The purpose of evaluating the ratio *k* is to determine a future human health impact given some new estimate of the prevalence of resistance in poultry carcasses. The product of this estimated prevalence with a forecast of the future poultry consumption level and the ratio k is equal to the expected number of affected people. If the acceptable threshold has been defined as a probability for some specific group, as discussed above, this number can be translated into the appropriate probability measure.

The parameter k relates the *current* propensity of a pound of fluoroquinolone-resistant *Campylobacter* contaminated poultry meat to cause human illness. It implicitly takes into account the variety of paths that a quantity of poultry meat took, including being thrown away, being well-cooked, some cross-contamination of other food products, etc. Radical change in the system would make the value of k irrelevant, for example, irradiation of food or any other system that would reduce the average *Campylobacter* load in contaminated carcasses. However, approximate corrections can be made to k to take account of such effects.

Defining a risk standard for assessing the microbial safety of new animal drugs

In the Framework Document, the Agency identified its goal as protecting the public health by ensuring that significant human antimicrobial therapies are not lost due to use of antimicrobials in food-producing animals, while providing for the safe use of antimicrobials in food-producing animals. Consistent with this goal, the Framework Document set out a categorization system for evaluating the microbial safety of antimicrobial drugs intended for use in food producing animals. In this document, the agency defined the potential human health impact associated with the use of an antimicrobial drug in food producing animals as the loss of effective drugs to treat human disease. The agency considered that evaluation would be made of the availability of effective alternative therapies to treat a particular disease.

Section 512 of the Federal Food, Drug, and Cosmetic Act, which establishes the conditions for approval of new animal drugs, requires that they be proven to be "safe." Even though section 201(u) of the Act provides that the use of the term "safe" in section 512 has reference to the health of man or animal, the term "safe" is not defined in section 512. Section 512 does require that determinations of safety include consideration of the probable consumption of the new animal drug and of any substance formed in or on food because of the use of the drug. Prior to the addition of section 512 to the Act by the Animal Drug Amendments of 1968, animal drugs were regulated under several sections of the Act. Substances formed in or on food due to the use of animal drugs were regulated under the food additive provisions in section 409 of the Act. Under section 409, such substances had to be shown to be safe. The term "safe" also is not defined in section 409 of the Act. Its legislative history, however, states, "safety requires proof of a reasonable certainty that no harm will result from the proposed use of the additive." H. Rept. No. 2284, 85th Cong., 2d. Sess. 4-5 (1958). The Animal Drug Amendments of 1968 merely consolidated all of the existing statutory authorities related to animal drugs into section 512 and the legislative history indicated that the consolidation in no way changed the authorities with respect to the regulation of new animal drugs. S. Rept. No. 1308, 90th Cong., 2d. Sess. 1 (1968).

While not appearing in the statute, a definition of "safe" or "safety" in the context of food additives has been established by regulation (21 CFR 570.3(i)), which states:

> "*Safe* or *safety* means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:
>
> (1) The probable consumption of the substance and of any substance formed in or on food because of its use.
> (2)The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
> (3) Safety factors which, in the opinion of experts…, are generally recognized as appropriate."

Therefore, the Agency routinely applies the "reasonable certainty of no harm" standard in determining the safety of substances formed in or on food as a result of the use of a new animal drug.

In applying that standard to new animal drug residues, the food safety assessments focus on identifying the hazard of the chemical to humans and controlling or limiting the exposure to the chemical. The hazard to humans is assessed by conducting a standard battery of toxicology tests in animals. These tests are designed to determine the dose that causes the adverse effect and the dose at which no drug effect is seen, i.e., the no observed effect level (NOEL).

The NOEL of the most sensitive effect from the most sensitive toxicology study is divided by a safety factor to determine an acceptable daily intake (ADI). A safety factor of 1000, the product of three factors, is generally applied to animal studies of 90-day duration. One 10-fold factor is used to account for the

uncertainty in extrapolating from animals to man. A second 10-fold factor is used to account for the variability among individuals and an additional 10-fold factor is used to extrapolate to a lifetime of exposure. The recent Food Quality Protection Act directed the EPA to impose an additional 10-fold safety factor for pesticides that are present in the diet of children. The amount of pesticide, food additive or drug residue permitted in the tissues of each edible commodity is based upon the quantity of food consumed daily by the 90th percentile consumer. For carcinogenic compounds used in food-producing animals, the agency allows an incremental risk of 1 in one million.

It is clear, however, that there is a significant difference between this traditional chemical residue-based determination of the safety of new animal drugs intended for food animal use and the determination of safety in the context of antimicrobial resistance. The former involves assessment of the risk of consumption of a chemical substance formed in or on food, i.e., residues of the new animal drug--a risk that is not anticipated to change appreciably over time, while the latter involves assessment of the risk of a "substance", i.e., resistant microbes, which will not be present in food as an immediate consequence of approval, but which may appear with increasing prevalence over time as the animal drug is used.

The Framework document acknowledges and attempts to provide a mechanism to deal with this non-traditional risk by establishing that the risk to be assessed is the potential loss of effective therapy for human microbial disease. It provides for assessment of this risk through an initial categorization process involving an assessment of the importance of various drugs or drug classes to the treatment of microbial disease in humans coupled with an estimation of the potential for exposure of humans to resistant microorganisms derived from animals. Depending on the initial categorization, it continues the assessment via pre-approval studies intended to elucidate both the potential for particular drugs to select for resistant bacteria in animals and the rate at which such selection might take place. It also contemplates the establishment of resistance and monitoring thresholds (via formal quantitative risk assessment or otherwise) against which the continued safety of the animal drug will be assessed post-approval and with respect to which mitigation efforts may ensue, up to the point of drug withdrawal if all else fails.

All of this is intended to adequately protect the public health while permitting the approval of drugs to protect animal health. Implicit in the Framework document is the application of the safety standard in a manner, which permits the implementation of the system proposed in this document to assure that the public health is protected by preserving the long-term effectiveness of antimicrobial drugs for treating diseases of humans. Therefore, in the context of the Framework document, requiring reasonable certainty that the public health will be protected as a condition of new animal drug approval (and subsequent use of the approved drug) does not necessarily equate to reasonable certainty that no individual will suffer any effect. Ensuring public health protection under the process proposed by the Framework document does require mechanisms to rapidly and effectively react to the results of post-approval monitoring, including one or more mechanisms to rapidly remove animal drugs from the market if the final safety threshold--the one which represents unacceptable risk to the public health--is exceeded.

Establishing Regulatory Thresholds

Once the risk standard is defined, the population of interest determined and the regulatory endpoint decided upon, this model might serve as a tool for establishing regulatory thresholds, a concept introduced in the Framework document. The FDA proposed to establish thresholds for the development of resistant bacteria in order to protect human health. There are two methods for establishing regulatory thresholds, technology-based and health-based. Technology-based thresholds are established by measuring the amount of contaminant currently present. For example, HACCP limits for *Salmonella* contamination on carcasses were established by measuring the current level of carcass contamination. If a qualitative risk assessment suggests that this amount represents an unacceptable risk then further regulatory action is taken. In the HACCP regulation, USDA concluded that the current food borne disease burden due to *Salmonella* was too high and required the levels on carcasses be lowered.

A more detailed quantitative assessment can be conducted to determine the magnitude of the risk or if strategies can be developed to decrease the amount of contamination or to prevent or control the development of resistance. For antimicrobial resistance in animal food borne pathogens, a threshold could

be established by measuring the amount of resistance present in the food borne pathogen for approved products or the amount projected to develop based on pre-approval studies. If this level represents an unacceptable public health risk, strategies can be developed to decrease the disease burden or resistance level. While technology-based thresholds have an advantage in ease of establishment, these values are not necessarily tied to public health outcomes.

Health-based thresholds are established based upon a quantitative risk or safety assessment. Since public health risk is a product of hazard and exposure, health-based thresholds are generally established by performing a comprehensive evaluation of both the hazard and exposure. Establishing health-based thresholds, however, is difficult and resource intensive due to the lack of quantitative data on public health outcomes related to the use of antimicrobials in food animals. Also, because of the uncertainty and quality of the data, some authors believe that health-based thresholds cannot be directly related to public health outcomes.

One approach would be to use a hybrid of the risk assessment approach and the safety factor approach to establish regulatory thresholds. For example, the complete risk assessment would be conducted for the pathogen that develops resistance the soonest (sentinel food borne pathogen) in the animal species associated with the most food borne disease due to that pathogen (the reference animal species). The model could then be used to determine when an unacceptable human health impact is reached (the resistance threshold); and to calculate the level of resistance permissible in the bacteria on the reference animal species at slaughter (monitoring threshold). This monitoring threshold could then be applied to all other species and be protective of the public health because the food borne disease burden from other species will be less than that in the reference species. For food borne pathogens with health impacts greater than that of the sentinel bacteria, it may not be possible to wait until resistance develops to assess the public health impact. In this case, a safety factor could be determined and applied to the monitoring threshold established for the sentinel bacteria to be protective of the public health. Mitigation action would be warranted when monitoring thresholds in either the sentinel or other food borne pathogens would be reached.

The agency believes that management of risk should be an ongoing process and not be initiated only when a monitoring threshold is reached. Comments at the Veterinary Medicine Advisory Committee in January 1999 and comments made to the Framework document docket expressed the need to implement judicious use principles in the selection and use of antimicrobial drugs in food-producing animals. The application of these principles is critical in managing the risk of antimicrobial resistance by limiting the use of important human antimicrobials in food-producing animals and thereby reducing the selection pressure for the development of resistance.

The Hazard Analysis Critical Control Points (HACCP) regulations being implemented by USDA/FSIS have reduced the incidence of bacteria isolated from carcasses at slaughter in the plants in which the regulations have been applied. While this risk assessment was appropriately designed to estimate risk to human health from resistant food borne pathogens associated with the use of antimicrobials in food-producing animals, the current apparent effect of the HACCP regulations is to reduce human exposure to *Campylobacter*, which should concurrently reduce illness in people. Therefore, this is another critical factor in the overall management of risk to the consumer.